

REMARKS

Claims 110-142 are pending in the subject application. Claims 141 and 142 are withdrawn from consideration by the Examiner as directed to a non-elected invention. By this amendment, Claims 134-137 have been amended. Applicant maintains that the amendments do not raise an issue of new matter. Support for the amendments can be found at least in the previous version of the claims. Entry of the amendments is respectfully requested.

Withdrawn Rejections

The previously issued obviousness-type double patenting rejection over U.S. Patent Application No. 10/752,965 and the previously issued rejection under 35 U.S.C. §112, first paragraph, have been withdrawn.

Rejections under 35 U.S.C. §112, Second Paragraph

Claims 134-137 are rejected for lacking antecedent basis for pharmaceutically acceptable salts of pipamperone or escitalopram. Reconsideration and withdrawal of this ground of rejection are respectfully requested in view of the amendments made herein above to Claims 134-137.

Rejections under 35 U.S.C. §103(a)

Claims 110-140 are rejected as being unpatentable over Cremers et al., WO 01/41701 in view of Van Oekelen et al. (Eur. J. Pharm. 425: 21-32, 2001) and further in view of Sanchez et al., WO 01/03694.

Applicants respectfully traverse this rejection.

The pending claims are directed to pharmaceutical compositions comprising pipamperone and escitalopram in specified dosage amounts. Applicant previously noted

that the U.S. Patent Office has acknowledged the nonobvious, unexpected results of the combination of low dose pipamperone and citalopram (in specified doses) (see in particular the detailed Reasons for Allowance in the Notice of Allowance dated June 23, 2010 in U.S. Patent Application No. 10/752,423, and also the Interview Summary dated June 6, 2010 in U.S. Patent Application No. 10/752,423 and the Interview Summary dated June 8, 2010 in U.S. Patent Application No. 10/725,965). Applicant further noted that escitalopram is the *S*-stereoisomer (enantiomer) of citalopram. Since those comments were made in July 2010, patent family member U.S. Patent Application No. 10/725,965 issued as U.S. Patent No. 7,884,096 on February 8, 2011 with claims directed to pharmaceutical compositions for treating a mood disorder or an anxiety disorder comprising: (a) pipamperone in a dose of 5-15 mg, (b) citalopram in a dose of 10-40 mg, and a pharmaceutically acceptable carrier. In addition, patent family member U.S. Patent Application No. 10/752,423 issued as U.S. Patent No. 7,855,195 on December 21, 2010 with claims directed to methods for treating an anxiety disorder in a patient comprising administering to the patient a pharmaceutical composition comprising i) pipamperone in a dose of 5-15 mg and ii) citalopram in a dose of 10-40 mg. As discussed in more detail below, citalopram is a racemic mixture comprising 50% of the active and hence pharmaceutically relevant enantiomer (*S*-citalopram) and 50% of the inactive and hence pharmaceutically irrelevant enantiomer (*R*-citalopram). Thus, the dose to be administered of escitalopram (*i.e.* the pure form of the pharmaceutically active *S*-enantiomer) is half of the dose to be administered of the racemic mixture citalopram (only consisting of half the amount of *S*-citalopram). Accordingly, citalopram in a dose of 10-40 mg corresponds to escitalopram in a dose of 5-20 mg. When administered to a patient in these respective doses, the plasma concentration of the clinically relevant form (*i.e.* the *S*-enantiomer) is the same for citalopram and escitalopram. Thus, the U.S. Patent Office has in essence already acknowledged the

patentability of the subject matter set forth in the present claims.

In the present Office Action, the Examiner asserts in essence that:

- (a) Cremers teaches the use of 5-HT_{2C} antagonists in a combination therapy with SSRIs (such as escitalopram) for the treatment of mood and anxiety disorders;
- (b) Cremers teaches that the 5-HT_{2C} antagonists can be administered in a dose range between 0.1 to about 150 mg/day;
- (c) Van Oekelen teaches that pipamperone is a 5-HT_{2C} antagonist; and
- (d) Sanchez teaches a dose of escitalopram between 10-20 mg for the treatment of neurotic disorders such as anxiety and panic disorders.

Hence, according to the Examiner, it would be *prima facie* obvious for a person skilled in the art to combine pipamperone in the claimed dose range with escitalopram for the treatment of mood and anxiety disorders.

The Examiner further asserts that the unexpected data with respect to the combination of pipamperone with citalopram do not translate to the combination of pipamperone and escitalopram.

In reply, applicant in addition respectfully notes the following.

The specified dose range of Cremers is not enabled

The Examiner is of the opinion that Cremers teaches the combination of SSRIs with 5-HT_{2C} antagonists for the treatment of (among others) anxiety, whereby the 5-HT_{2C} antagonists can be administered in a dose range of 0.1 to about 150 mg daily.

Applicant notes that the dose of 5-HT_{2C} antagonist to be administered depends on the specific drug and hence will have to be determined on an individual basis. A potent drug will need to be administered at a lower dose than a less potent drug. As such, there is no specific guidance in Cremers as to the specific dose range for each individual drug. The only guidance Cremers provides is that the drug needs to be a 5-HT_{2C} antagonist.

Therefore, from Cremers, any drug which is to be administered at least needs to possess a 5-HT_{2C} antagonistic activity at the administered dose. If administered below this dose, there is not 5-HT_{2C} antagonistic activity, hence there is no point in administering the drug at all. Thus, Cremers teaches administering a drug in a **dose sufficient for 5-HT_{2C} antagonistic activity** to occur, which for some drugs will be a higher dose than for other drugs.

Cremers defines 5-HT_{2C} antagonists in respect to receptor affinity

While not being enabled in respect of the dose range of the 5-HT_{2C} antagonist, Cremers does however specify the 5-HT_{2C} antagonist to be administered in respect of its affinity for the 5-HT_{2C} receptor. In paragraph [0058] of Cremers, it is specified that useful drugs need to have a K_i value below 30 nM for the 5-HT_{2C} receptor. Cremers thus teaches that for the treatment of anxiety and mood disorders, the SSRI needs to be combined with a drug which has a K_i for the 5-HT_{2C} receptor below 30 nM. In other words, a K_i below 30 nM classifies a drug as a 5-HT_{2C} antagonist.

Pipamperone is not a 5-HT_{2C} antagonist as specified by Cremers

If one looks at the K_i value of pipamperone for the 5-HT_{2C} receptor, it becomes clear that pipamperone does not fall within the definition of a 5-HT_{2C} antagonist as specified by Cremers. From the publication of Leysen (Int J Psychiatry Clin Pract, 2:S3-S17; of record), it is clear that the pK_i of pipamperone for the 5-HT_{2C} receptor is -6.92. Hence, the K_i of pipamperone for the 5-HT_{2C} receptor is 120 nM. As the K_i of pipamperone for the 5-HT_{2C} receptor is much higher than the required K_i in Cremers, it is apparent that pipamperone does not qualify as a valid 5-HT_{2C} antagonist according to Cremers. In this regard, it may even be argued that Cremers teaches against the use of pipamperone for combined use with an SSRI in the treatment of mood and anxiety

disorders. The teachings of Cremers in fact support the idea that a high dose of pipamperone in effect is a **different drug** than a low dose of pipamperone, due to different receptor binding affinities, inevitably leading to a different effect of the drug.

Moreover, the Examiner states on page 8, lines 13-17 of the present Office Action that:

*“While Cremers et al. does not explicitly teach pipamperone as the 5-HT_{2C} antagonist, it is taught that the composition is comprised of a compound that **functions** as a 5-HT_{2C} antagonist, partial agonist or inverse agonist (Abstract), and that this compound includes “antipsychotics having effect at 5-HT_{2C} receptors” (p. 12, lines 10-18).”* (Emphasis added)

This statement actually corroborates the above arguments, in that the Examiner actually acknowledges and admits that for a compound to be useful it has to be **able to function** as a 5-HT_{2C} antagonist. In contrast herewith, and as demonstrated above, **pipamperone at the claimed dose is not able to function as a 5-HT_{2C} antagonist.**

Van Oekelen teaches a high dose of pipamperone

Given that receptor occupancy (and hence the effect of a drug) is related to the affinity of the drug for the receptor (K_i) as well as the administered dose, it can be reasoned that a drug with a low affinity for the receptor (*i.e.* a high K_i) may reach the required receptor occupancy for a clinical effect to occur when such drug is administered at a high enough dose. This would be exactly the case for pipamperone in respect of the 5-HT_{2C} receptor. As pipamperone has a low affinity for the 5-HT_{2C} receptor (and is not even classified as a useful 5-HT_{2C} antagonist according to Cremers), for any relevant

clinical effect to occur, one would have to substantially increase the dose.

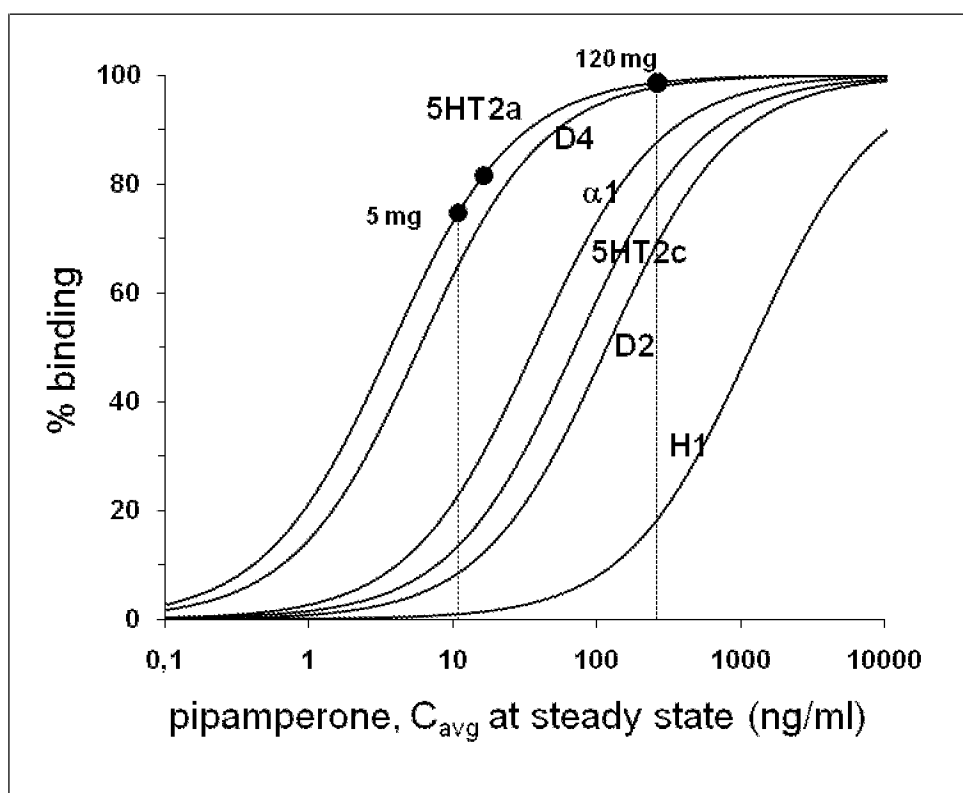
A high dose of pipamperone to achieve a 5-HT_{2C} antagonistic activity/effect is exactly what Van Oekelen teaches. Van Oekelen discloses 5-HT_{2C} antagonistic activity of pipamperone at a dose well above the claimed low dose of pipamperone. From Figure 3 of Van Oekelen, it is clear that to achieve a full effect of pipamperone on the 5-HT_{2C} receptor (*i.e.* an inhibition of stimulation of the receptor by serotonin), a markedly higher pipamperone dose is required than for the same effect to be achieved on the 5-HT_{2A} receptor. Full effect on the 5-HT_{2C} receptor is achieved at a dose of 10 μ M, whereas full effect on the 5-HT_{2A} receptor is achieved at a dose of 100 nM, *i.e.* a dose which is a 100 fold lower (see also page 27, left column, last sentence of Van Oekelen). In this respect, Van Oekelen explicitly acknowledges that a high dose of pipamperone was used in their (*in vitro*) experiments to eliminate affinity-dependent effects, as indicated on page 29, right column, end of first paragraph of Van Oekelen, reproduced below:

“We chose 10 μ M 5-HT or pipamperone as the modulatory ligand concentration to investigate the agonist- and antagonist-mediated regulation of rat 5-HT_{2A} or 5-HT_{2C} receptors, to exclude the influence of differences in affinity and to use a saturating concentration to reach total receptor occupancy for both receptors.”
(emphasis added)

Note that Van Oekelen discloses a concentration of pipamperone, rather than an absolute dose to be administered, as is the case in the instant application. Although not strictly comparable, applicant believes that the PK/PD (pharmacokinetics/pharmacodynamics) modeling for pipamperone in this respect allows one to correlate both parameters, as detailed below.

From PK/PD modeling, it is clear that that the claimed pipamperone dose of 5-15

mg daily corresponds to an average plasma concentration of 5-16 ng/ml. The PK/PD model can be found in the enclosed poster presented by Buntinx *et al.*, Selective Serotonergic Properties of Low-Dose Pipamperone May Enhance Antidepressant Effect: Preclinical Evidence (poster presented during the Society of Biological Psychiatry 65th Annual Meeting, held on May 20–22, 2010 in New Orleans, LA). For convenience, the PK/PD modeling figure is also shown below.



The PK/PD model clearly indicates that at the presently claimed low dose of pipamperone, no relevant 5-HT_{2c} receptor occupancy occurs.

Since the experiments of Van Oekelen were performed *in vitro*, applicant believes that comparing the concentration as taught by Van Oekelen with the plasma concentration as anticipated by the PK/PD modeling is justified (*i.e.*, both cases relate to a directly available and effective pipamperone concentration). Given the molecular

weight of pipamperone (MW = 375.48), a concentration of 5-16 ng/ml corresponds to 13.3-42.6 nM. Compared to the concentration as taught by Van Oekelen (10 μ M) it is clear that the claimed dose is between 250 and 750 times lower. Keeping in mind that Van Oekelen teaches that a fully effective dose is only reached at 10 μ M, it is clear that the claimed pipamperone dose does not qualify as having an effect on the 5-HT_{2C} receptor. This finding is further supported by Table 3 of Van Oekelen, which shows that no inhibition of the stimulation of the 5-HT_{2C} receptor by serotonin occurs at the claimed low dose of 13.3-42.6 nM (corresponding to 5-15 mg). Moreover, given the teachings of Van Oekelen (*i.e.* a pipamperone concentration of 10 μ M is needed for a full effect to be achieved), it can be seen from the PK/PD modeling that such concentration corresponds to a pipamperone concentration of 3754.8 ng/ml, corresponding to well above the conventional pipamperone dose of 120 mg.

Hence, from the above it is clear that the disclosed pipamperone dose/concentration by Van Oekelen is manifold higher than the claimed pipamperone dose/concentration.

The present invention is not obvious over the cited prior art

In conclusion, applicant respectfully maintains that the Examiner incorrectly cites Cremers and Van Oekelen in support of an obviousness rejection for the following reasons:

- (a) Cremers teaches that 5-HT_{2C} antagonists need to have a K_i below 30 nM; however
- (b) Leysen teaches that the K_i of pipamperone for the 5-HT_{2C} receptor is 120 nM; thus
- (c) pipamperone does not qualify as a bonafide 5-HT_{2C} antagonist; moreover
- (d) Van Oekelen teaches that if pipamperone is to be used as a 5-HT_{2C} antagonist, then the dose needs to be increased.

Applicant maintains that the arguments elaborated above demonstrate that the cited

references (Cremers and Van Oekelen) not only are irrelevant for the present invention, but that in fact the cited references even teach away from the present invention. Applicant further maintains that the additional citation of Sanchez by the Examiner in this respect is irrelevant. Sanchez may indeed disclose that escitalopram can be used in a dose of 10-20 mg for the treatment of among others anxiety and panic disorders. However, Sanchez does not disclose or suggest the combined use of pipamperone and escitalopram, let alone at the claimed low dose of pipamperone.

Extrapolation of the unexpected effects of citalopram to escitalopram

According to the Examiner, the showing of unexpected results for the combination of low dose pipamperone and citalopram is not found to be applicable to the instant claims, although the Examiner acknowledges that escitalopram is the S-enantiomer of citalopram.

Applicant notes that citalopram is a 1:1 racemic mixture of R-citalopram and S-citalopram (escitalopram). As evidenced by Hyttel *et al.* (J Neural Transm, 1992, 88:157-160), attached herewith, S-citalopram is the pharmaceutically active enantiomer. On page 158, first paragraph of the results of Hyttel states:

“The eutomer (the more potent enantiomer) (S)-(+)-citalopram is equipotent with citalopram on 5-HT uptake in vitro (Table 1).”

And further on page 159, last paragraph of the results of Hyttel states:

“In the 1-5-HTP potentiation tests (S)-(+)-citalopram is equipotent with or slightly more potent than citalopram whereas the distomer (R)-(-)-citalopram is inactive (Table 2).”

Hyttel concludes on page 160, last paragraph:

“As the inhibition of 5-HT uptake seems to be the only mechanism of action to explain citalopram's pharmacological and clinical effects it is assumed that the presence of the distomer in the racemate (citalopram) probably does not contribute to the antidepressive effect of citalopram.”

Accordingly, citalopram as a racemic mixture comprises 50% of the active and hence pharmaceutically relevant enantiomer (S-citalopram) and 50% of the inactive and hence pharmaceutically irrelevant enantiomer (R-citalopram). The daily dose to be administered of escitalopram (*i.e.*, the pure form of the pharmaceutically active S-enantiomer) is half of the dose to be administered of the racemic mixture citalopram (only consisting of half the amount of S-citalopram). Whereas citalopram needs to be administered in a dose, for example, between 20-40 mg daily, escitalopram needs to be administered in a daily dose of 10-20 mg to be comparable. When administered to a patient in these respective doses, the plasma concentration of the clinically relevant form (*i.e.* the S-enantiomer) is the same for citalopram and escitalopram.

In view of the above, the skilled person would not expect a different effect of pipamperone with citalopram versus escitalopram, all the more in view of the mode of action of pipamperone with (es)citalopram. In particular, (es)citalopram inhibits the reuptake of serotonin in the synapse, as a consequence of which synaptic serotonin concentrations rise. This leads to an increased serotonin receptor activation, of which receptors the activation of the 5-HT_{1A} receptor is clinically relevant for the treatment of mood and anxiety disorders. The activation of the 5-HT_{1A} receptor is however blocked by a negative feedback loop via activation of the 5-HT_{2A} receptor, thereby counteracting the

clinical effect. Pipamperone, as a specific inhibitor of the 5-HT_{2A} receptor, disinhibits the blockage of the 5-HT_{1A} receptor by preventing 5-HT_{2A} receptor activation, thereby potentiating the clinical effects of serotonin reuptake inhibitors, such as (es)citalopram.

Hence, a patient having received either citalopram or escitalopram in a dose giving rise to identical plasma concentrations of the clinically active S-enantiomer would experience the above described inhibition of the 5-HT_{1A} receptor via the 5-HT_{2A} receptor mediated feedback loop to the same extent. Accordingly, the effect of pipamperone (*i.e.* disinhibition of the 5-HT_{1A} receptor via 5-HT_{2A} receptor blockage) is identical, irrespective of whether citalopram or escitalopram has been initially administered.

Reconsideration and withdrawal of this ground of rejection are respectfully requested.

Status of U.S. Patent Family Members

Applicant would like to advise the Examiner of the status of U.S. patent family members.

1. U.S. Patent Application No. 10/725,965, filed December 2, 2003, now U.S. Patent No. 7,884,096, issued February 8, 2011. The issued claims are directed to pharmaceutical compositions for treating a mood disorder or an anxiety disorder comprising: (a) pipamperone in a dose of 5-15 mg, (b) citalopram in a dose of 10-40 mg, and a pharmaceutically acceptable carrier.

2. U.S. Patent Application No. 10/752,423, filed January 6, 2004, now U.S. Patent No. 7,855,195, issued December 21, 2010. The issued claims are directed to methods for treating an anxiety disorder in a patient comprising administering to the patient a pharmaceutical composition comprising i) pipamperone in a dose of 5-15 mg and ii) citalopram in a dose of 10-40 mg.

3. U.S. Patent Application No. 10/803,793, filed March 18, 2004, now

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abandoned.

4. U.S. Patent Application No. 10/984,683, filed November 9, 2004, now abandoned.
5. U.S. Patent Application No. 12/924,615, filed September 30, 2010, pending.
6. U.S. Patent Application No. 12/931,313, filed January 26, 2011, pending.
7. U.S. Patent Application No. 13/065,638, filed March 25, 2011, pending.

Request for Consideration of Withdrawn Subject Matter

The pending claims are directed to pharmaceutical compositions and uses of the compositions. Upon the finding of allowability of a product claim, applicant requests that the Examiner rejoin and consider process claims that depend from the allowed product claim.

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CONCLUSIONS

In view of the preceding amendments and remarks, applicants respectfully request that the Examiner reconsider and withdraw the rejections in the July 28, 2011 Office Action, and earnestly solicit allowance of the pending claims. If there is any minor matter preventing the allowance of the subject application, the Examiner is requested to telephone the undersigned attorney.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required with this reply or to maintain the pendency of the subject application, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 01-1785.

Respectfully submitted,

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